Tachykinin

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SUBSTANCE P INDUCES PROLIFERATION OF HUMAN T-LYMPHOCYTE PROLIFERATION: SELECTIVE EFFECT ON THE IL-2 SYSTEM. C. Brodie. Department of Life Sciences, Bar-Ilan University, Ramat-Gan 52900, ISRAEL.

In vivo and in vitro studies support the hypothesis that there is a complex bi-directional relationship between the nervous and the immune systems. This neuro-immunoregulatory interaction involves the existence of neurotransmitter and neuropeptide receptors on lymphoid cells, and those of lymphokines on cells of the nervous system. Receptors for neuropeptides such as substance P, VIP and somatostatin have been described on a variety of lymphoid cells. We examined the effect of substance P on human T cell proliferation and found that it exerted a dose-dependent increase in the proliferation of T cells activated with either suboptimal concentrations of PHA or with anti-CD3. To further define the target of substance P mediated T cell proliferation we took advantage of the ability to dissociate the first (competence, acquisition of IL-2 responsiveness) and second (progression) phases of mitogen-induced T cell proliferation. Substance P induced a small degree of competence in the presence of PDB but not in the presence of ionomycin. Thus, addition of IL-2 induced cell proliferation. Addition of substance P alone during the progression phase did not increase cells proliferation. However, concomitant addition of IL-2 and substance P increased cell proliferation beyond that obtained with IL-2 alone. Substance P increased in a dose-dependent manner the secretion of IL-2 and expression of p55 subunit of the IL-2R on PHA-activated T cells, whereas, it did not effect the secretion of IL-4 and the expression of IL-4R on activated T cells. The stimulatory effect of substance P was receptor-dependent since it was blocked by the receptor antagonists. These results provide evidence for the immunoregulatory role of tachykinin receptors in the function of human T lymphocytes and suggest that substance P may have differential effects on Th_1 and Th_2 cells.

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CHARACTERIZATION OF GUINEA PIG NK-1 RECEPTORS USING THE POTENT ANTAGONIST LIGAND, [^{3}H]-LY303870. D.R. Gehlert*, D.A. Schober, P.A. Hipskind, J. Nixon, B.D. Gitter, J.J. Howbert. Central Nervous System Research, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN 46285 U.S.A.

The neuropeptide, substance P (SP), produces its biological responses by binding to NK-1 receptors found in the brain and periphery. In general, the binding properties of the NK-1 receptor have been characterized using radiolabeled SP or SP analogs. Until recently, no useful antagonist radioligands were available for the study of these receptors. [^{3}H]-CP-96,345 and the related ligand, [^{125}I]-L-703606, have been introduced, but may interact with non-NK-1 sites. Another radioligand, [^{3}H]-99,994 appears to bind to a single site in guinea pig striatum. Recently, another class of nonpeptide NK-1 antagonists have been discovered. In the present study, we used a radiolabelled form of the NK-1 antagonist, LY303870, for use in homogenate and autoradiographic binding studies.

[^{3}H]-LY303870 rapidly associated with guinea pig striatal membranes and readily dissociated upon addition of unlabeled LY303870. Under equilibrium conditions, the ligand bound to a single site with a K_d of 0.22 nM and a B_{max} of 22 fmoles/mg protein. (±)CP-96,345, LY303870 and the related antagonist LY306740 were the most potent inhibitors of binding tested. While the nonpeptide antagonists had Hill coefficients near unity, peptide agonists were generally less potent and exhibited biphasic displacement curves. Consistent with binding to a G-protein coupled receptor, 10 µM Gpp(NH)p shifted inhibition by SP to a single, lower affinity site. The dissociation of specific [^{3}H]-LY303870 binding was unaffected by the presence of 10 µM Gpp(NH)p.

Autoradiographic studies were conducted using sections from guinea pig forebrain and brainstem. Adjacent sections were labeled with either [^{3}H]-LY303870 or [^{3}H]-SP. The distribution of binding sites for these ligands was similar. The highest levels of specific binding were seen in noradrenergic areas such as the locus coeruleus and bed nucleus of the stria terminalis while lower levels were seen in areas such as the striatum and dorsal horn of the spinal cord.

In conclusion, [^{3}H]-LY303870 binds with high affinity and selectivity to NK-1 receptors in guinea pig brain. This radioligand should provide a useful tool for the further study of mammalian NK-1 receptors.

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